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Strategies Followed for the Assessment of the Advanced Therapies by European Medicines Agency

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Abstract

The present study intended at the responsibility and strategies of European Medicines Agency which is a decentralised bureau of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the European Union. The study carried out on the role of European Medicines Agency in the advanced therapies and ensure the assessment of European Medicines Agency in the evaluation of Advanced therapy Medicinal Products and to study the independence of its scientific assessments towards its open and translucent policy. It was focused on its scientific expertise together in the framework of European medicines regulatory network and the procedure of team work and commitment of the Committee in agreement with the regulations following GMP, GCP and GLP. Ultimately, the complete support and guidance given to the Companies researching, developing and manufacturing Advanced Therapy Medicinal Products.

Keywords: European medicines • Scientific evaluation • Public health

Introduction

The European Medicines Agency (EMA) is a decentralised bureau of the European Union (EU) accountable for the scientific evaluation, regulation and safety monitor of medicines in the European Union. The agency is governed by an self-governing Management Board. Its day-to-day operations are accepted out by the EMA staff, overseen by EMA's Executive Director. EMA is a networking organization whose deeds involve many experts from across Europe. These experts carry out the work of EMA's scientific committees [1].

Objectives and rationale of EMA

Work strategy:

- To accomplish its assignment, the EMA works intimately with national competent authorities in a authoritarian network.
- The Agency also implements policies and procedures to certify it works independently and upholds the highest standards in its systematic recommendations.
- It brings together the scientific expertise by working closely with the national regulatory authorities in European Union (EU) Member States, in a joint venture known as the European medicines regulatory network.
- The network pools resources and expertise in the EU and gives EMA access to European scientific experts in the bylaw of medicines.
- Ensuring the independence of its scientific assessments is a high precedence for the body.
- The Agency takes care to ensure that its scientific experts, staff and Management Board do not have any financial or other interests that could affect their impartiality.
- EMA strives towards being as open and transparent as possible about how it reaches its scientific conclusions. EMA's European public assessment reports describe the scientific basis for EMA's recommendations on all centrally authorised medicines.
- EMA also publishes a large amount of information in lay language about its work and about medicines. For more information, see Transparency.
- The Agency also seeks to publish clear and up-to-date information on how it operates, including planning and reporting documents and information on funding, financial management and budgetary reporting [1,2].

Times past and timelines: Time-honoured in 1995, the European Medicines Agency (EMA) has worked across the European Union (EU) and worldwide to guard public and animal health by assessing medicines to painstaking scientific standards and by providing partners and stakeholders with independent, science-based information on medicines.

It has a 25-year track record of ensuring efficacy and safety of human and veterinary medicines across Europe and promoting research and novelty in the development of medicines. EMA's success is based on cooperation within the European medicines regulatory network:

- An exclusive partnership connecting the European Commission, the medicines regulatory authorities in the European Economic Area countries and EMA.
- Working collectively has expectant the exchange of knowledge, ideas and best practices, in order to ensure the highest standards in medicines regulation.
- Today, seven EMA scientific committees and more than 30 working parties provide scientific expertise for the regulation of medicines by drawing on a pool of several thousand European scientific experts from the network.

Milestones and achievements: EMA was set up in 1995 to harmonise the work of existing national medicine regulatory bodies.

- The Agency's remit has expanded over time, in line with new EU

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legislation. On top of its remit to evaluate human and veterinary medicines.

- EMA is also responsible for products developed in the specialised areas of medicines for rare diseases (since 2000), herbal medicines (from the time when 2004), medicines for children (seeing as 2006) and advanced-therapy medicines (ever since 2007).
- Acquiring these responsibilities resulted in new scientific committees which provide the expertise in these areas.
- With the establishment of the Committee for Orphan Medicinal Products in 2000, EMA opened its doors to patients and healthcare professionals. Today, their representatives take part in most of EMA's scientific committees as full members, adding their unique perspective and experiences to discussions.
- They play an increasingly important role in the assessment of the risks and benefits of medicines.
- In 2014, patients discussed the benefit-risk evaluation of a medicine within the Committee for Medicinal Products for Human Use (CHMP) for the first time.
- With the creation of the Pharmacovigilance and Risk Assessment Committee (PRAC) in 2012, EMA started to play an even more important role in monitoring the safety of medicines across Europe.
- As of January 2015, EMA has been implementing its landmark policy on publishing the clinical data that underpin European decision-making on medicines.
- This will provide an unprecedented level of transparency for patients, healthcare professionals, academia and industry.

25 years of European medicines agency-timeline

Fostering scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union, the timelines are shown in table 1.

The European Medicines Agency (EMA) has seven scientific committees and many working parties, related groups which carry out the scientific work of the Agency. The committees along with working parties also contribute to the improvement of medicines and medicine regulation, by: providing scientific advice to companies researching and developing new medicines; preparing scientific guidelines and regulatory guidance to help pharmaceutical companies prepare marketing authorisation applications; contributing to the harmonisation of regulatory requirements on the EU and internationally.

EMA's committees:

- Committee for medicinal products for human use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for medicinal products for veterinary use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on herbal medicinal products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO)

Composition of committees and working parties: EMA's committees, working parties and related groups are composed of European experts made available by national competent authorities of the EU and EEA Member States.

Adopting a committee opinion or recommendation: EMA committees each have their own rules of procedure. To carry out a scientific assessment, usually a committee appoints a rapporteur to prepare an appraisal report, which the committee will regard as and eventually adopt as part of a scientific opinion or recommendation. For certain procedures, a 'co-rapporteur' also prepares an assessment independently from the rapporteur. An assessment team supports the rapporteur and co-rapporteur with necessary expertise and resources. The EMA secretariat provides technical, scientific and administrative support for each assessment.

Table 1. Timeline of EMA.

Year	Scientific Excellence-activity
1995	EMA time-honoured Foremost centrally authorised human medicine
1996	Start on of international harmonisation programme for pharmaceuticals First centrally authorised veterinary medicine
2000	Orphan Medicines Regulation
2001	First two orphan medicines Clinical Trials ordinance
2004	reassess of EU pharmaceutical legislation
2005	Herbal Medicines Directive SME office established SME regulation
2006	earliest two biosimilar medicines Paediatric Medicines Regulations First conditional endorsement
2007	First centrally authorised generic medicine
2009	Minor-use-minor-species inadequate-market policy First marketing sanction for an Advanced Therapy Medicinal Product
2010	New Pharmacovigilance legislation
2011	First paediatric-use marketing approval Falsified Medicines ordinance Initial ESVAC report
2012	First gene-therapy medicine
2014	First stem-cell medicine
2015	primary joint strategy of EMA and national medicines authorities
2016	Proactive periodical of clinical data Initiate of PRIME (Priority Medicines) scheme
2017	Amsterdam is announced as EMA's new address Mutual appreciation harmony on inspections First public consideration
2018	First two CAR-T medicines New Veterinary Medicines Regulation
2019	First vaccine against Ebola EMA elected as ICMRA chair
2020	Relocation to the Netherlands completed

A peer-review process provides additional quality assurance of definite scientific assessments: EMA committees act by consensus whenever possible and holds a vote. It may exclude committee members from voting on specific issues, in accordance with EMA's policy on handling competing interests. The working language of all of the EMA committees is English including plenary discussions, working documents and further correspondence. The agency does not endow with interpretation and translation services. Further any financial remunerations are carried out by their staff on behalf of the EMA committees (e.g. as rapporteurs or experts), in the framework of Fees payable to EMA Rapporteurs and co-rapporteurs can launch multinational assessment teams with experts from other Member States along with their home originated members. This is proposed to assemble the best expertise for medicines evaluation despite of geographically based experts. EMA coordinates inspections for human and veterinary medicines authorised under the centralised procedure or in the context of a referral, on appeal from the committee for medicinal products for human use (CHMP) or committee for medicinal products for veterinary use (CVMP). EMA does not conduct inspections itself but requests that the inspection be carried out by national authorities in the EU Member States. EMA is the primary contact point for reporting a suspected quality defect with any centrally authorised product and is responsible for coordinating the investigation, evaluation and follow-up of such cases. The agency also operates a Sampling and testing programme to authenticate the quality of centrally authorised medicines placed on the market and to check their compliance with their authorised specifications. In addition, EMA plays a key role is in coordinating and harmonising EU-wide activities, including:

- Developing and harmonising standards at EU level
- Developing EU guidelines on inspections and related procedures
- Preparing guidance through inspectors working groups
- Coordinating advice on the interpretation of regulatory requirements

Aim

To study the role of European Medicines Agency in the advanced therapies and warrant the assessment of European Medicines Agency in the assessment of Advanced therapy Medicinal Products and to study the independence of its scientific assessments towards its open and translucent policy.

Objectives

- To study the European Medicines Agency with its scientific expertise together in the framework of European medicines regulatory network.
- To emphasize the team work and commitment of the Committee in accordance with the regulations following GMP, GCP and GLP.
- To study the complete support and guidance given to the Companies researching, developing and manufacturing Advanced Therapy Medicinal Products.

Methodology

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury.

ATMPs can be classified into three main types:

- **Gene therapy medicines:** these include genes for a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a range of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.
- **Somatic-cell therapy medicines:** these have cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.
- **Tissue-engineered medicines:** these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

Definitions of the different groups of advanced therapy medicinal products

Medicinal product: Any substance or combination of substances accessible as having properties for treating or preventing disease in human beings; or Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Immunological medicinal product: Any medicinal product consisting of vaccines, toxins, serums or allergen products: Vaccines, toxins and serums shall cover in particular:-

- Agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine
- Agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin
- Agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin

Allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

Advanced therapy medicinal product: A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European parliament and of the council of 13 November 2007 on advanced therapy medicinal products.

Homeopathic medicinal product: Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

Medicinal products derive from human blood or human plasma: Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.

Recent directions by the European Medicines Agency (EMA)

- In April 2020, EMA's Committee for Advanced Therapies (CAT) advised patients and the general public to beware of unproven cell-based therapies.
- This followed the appearance of advertisements for cell therapies as cures for serious conditions across the European Union in early 2020.
- In its statement, the CAT warned against the use of unregulated cell-based therapies, which may be ineffective and increase the risk of serious adverse reactions.
- EMA presages contrary to using unproven cell-based therapies.

EMA's Committee for Advanced Therapies (CAT) is advising patients and the general public against using unregulated cell-based therapies which may not be safe or effective.

- The CAT's advice is in response to individuals, companies and hospitals promoting unproven cell-based therapies as cures for a broad range of conditions including cancer, cardiovascular diseases, autism, cerebral palsy, muscular dystrophy and vision loss.
- These treatments can pose serious risks to patients for little or no benefit. Patients using unproven or unregulated cell-based therapies have reportedly suffered serious, sometimes fatal, side effects including infections, unwanted immune reactions, tumour formation, loss of vision and bleeding in the brain. Cell-based therapies are treatments using cells from the patient or a donor.
- The use of blood and cells for transplantation is a well-established medical practice. However, if cells are not used for the same essential function in the recipient as in the donor or if they are being substantially manipulated, they are not considered transplants and their safety and benefits cannot be assumed. For this reason, such therapies are regulated in the EU as medicinal products.
- Rapidly evolving technology in the field of cell-based therapy brings exciting new opportunities for treating a range of diseases, including many currently considered incurable.
- The CAT emphasises that for patients to benefit from the promise of cell-based therapies, well designed clinical trials on the safety and benefits of cell-based therapies are essential. Such trials are not only necessary for understanding the safety and benefits of innovative therapies; they also protect the safety, dignity and rights of patients.
- Well-designed clinical trials also keep patients informed about the potential benefits and risks of the treatments and can be used to support authorisation in the EU, which will ultimately benefit more patients.

Table 2. Advanced therapies in the product life cycle.

I-Research and Development	II-Marketing Authorization	III-Post Authorization
A. Support for Advanced therapy developers	A. Advanced therapy Classification	A. Pharmacovigilance for advanced therapies
B. Scientific guidelines	B. Marketing authorization procedures for advanced therapy medicinal products	

- When evaluating the data arising from clinical trials of cell-based medicines, the CAT also checks that the quality of these products is properly controlled. Once the products are authorised in the EU, EMA and national medicines authorities monitor their safety continuously and share information to enable them take rapid EU-wide decisions to protect patient's health.

- Circumventing the marketing and clinical trial authorisation procedures makes it difficult to understand and document the effects of cell-based therapies, thereby depriving future patients of access to potentially curative treatments.

Role of Committee of Advanced Therapies (CAT)

- The CAT will continue its work in helping the development of new cell-based and other advanced therapies with the goal of increasing timely access to these potentially life-changing treatments.

- Patients or their families who are considering cell-based therapies should ask their healthcare professional about the benefits and risks of the treatment and which authority has approved it. They can also contact their national medicines authority or EMA directly.

Responsibilities of cat in the risk management of ATMPs

- CAT advises all the healthcare providers to explain the benefits and risks of the cell-based therapies that they are providing to patients, as well as confirming that regulatory authorities have approved their use.

- The CAT's statement replaces a statement it issued in 2010 following reports of unregulated stem-cell therapies being offered to patients.

Product life cycle of advanced therapies

The advanced therapies are categorized into three sections by the CAT for the ease of assessment and post marketing authorizations as shown in table 2.

Advanced therapies-research and development

Support for advanced therapy developers: Research Investigators or Sponsors or Developers of advanced therapy medicinal products (ATMPs) must be familiar with the legislation governing different stages of the medicine development process, including

Good Manufacturing Practice (GMP),

Good Clinical Practice (GCP) and

Good Laboratory Practice (GLP) requirements.

The European Medicines Agency (EMA) offers a range of advisory services and incentives to support the development of ATMPs.

GMP requirements

Developers of ATMPs need to be aware of the legislation that is applicable to different stages of the process.

- Utilisation of substances of human origin such as blood, tissues and cells in the manufacture of an ATMP requires compliance with relevant legislation (Directive 2002/98/EC and associated implementing directives and Directive 2004/23/EC and associated implementing directives) in relation to procurement, donation and testing.

- Subsequent manufacture of ATMPs must be performed in compliance with Directive 2001/83/EC and in line with the GMP guidelines

ATMPs specific GMP strategy

EMA endows with official support to developers by their:

- Scientific advice and protocol assistance
- Orphan designation
- The micro, Small and Medium-sized Enterprise (SME) office
- Classification of Advanced Therapy Medicinal Products (ATMPs)
- Certification of quality and non-clinical data for SMEs

The legislation provides for scientific and financial incentives to encourage research and development in the area of advanced therapies. Developers of ATMPs can get hold of reductions in the fees payable to EMA of:

- 65% fee reduction for a request for scientific advice for ATMPs (90% for SMEs)
- 90% fee reduction for the certification procedure

Scientific course of action on good manufacturing practice particularly to advanced therapy medicinal products:

- Acquiescence with good manufacturing practice ("GMP") is mandatory for all medicinal products that have been granted a marketing authorisation. Likewise, the manufacture of investigational medicinal products must be in accordance with GMP. Advanced therapy medicinal products that are administered to patients under Article 3(7) of Directive 2001/83/EC1 (so called "hospital exemption") must be manufactured under equivalent quality standards to the manufacturing of advanced therapy medicinal products with a marketing authorisation.

- These strategies develop the GMP requests to be applied in the manufacturing of ATMPs that have been granted a marketing authorisation and of ATMPs used in a clinical trial setting. These Guidelines do not apply to medicinal products other than ATMPs. In turn, the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC4 and Article 63(1) of Regulation (EU) No 536/2014 do not apply to ATMPs, unless specific reference thereto is made in these Guidelines.

General principles:

- Quality plays a major role in the safety and efficacy profile of ATMPs. It is the responsibility of the ATMP manufacturer to ensure that appropriate measures are put in place to safeguard the quality of the product (so-called "pharmaceutical quality system"). Pharmaceutical quality system' means the total sum of the arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use.

- The size of the company and complexity of the activities should be taken into consideration when designing a pharmaceutical quality system. Senior management should be actively involved to ensure the effectiveness of the pharmaceutical quality system. While some aspects may be company-wide, the effectiveness of the pharmaceutical quality system is normally demonstrated at site level.

- Compliance with Good Manufacturing Practice ("GMP") is an essential part of the pharmaceutical quality system.

- In particular, through the pharmaceutical quality system it should be ensured that:

I. The personnel are adequately trained and there is clear allocation of responsibilities.

II. The premises and equipment are suitable for the intended use and that there is appropriate maintenance thereof.

III. There is an adequate documentation system that ensures that appropriate specifications are laid down for materials, intermediates, bulk products and the finished product, that the production process is clearly understood and that appropriate records are kept.

IV. The manufacturing process is adequate to ensure consistent production (appropriate to the relevant stage of development), the quality of the product and the compliance thereof with the relevant specifications.

V. There is a quality control system which is operationally independent from production.

VI. Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory requirements (i.e. variations procedure in the case of authorised ATMPs, or authorisation procedure of a substantial modification of a clinical trial in the case of investigational ATMPs) and for the evaluation of changes implemented.

VII. Quality defects and process deviations are identified as soon as possible, the causes Investigated and appropriate corrective and/or preventive measures are taken; and (viii) adequate systems are implemented to ensure traceability of the ATMPs and of their starting and critical raw materials.

- A continuous assessment of the effectiveness of the quality assurance system is important. Results of parameters identified as a quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. The manufacturer should conduct self-inspections as part of the pharmaceutical quality system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures and/or preventive actions. Records should be maintained of such self-inspections and any corrective actions subsequently taken.

- In the case of authorised ATMPs, quality reviews should be conducted annually to verify the adequacy and consistency of the existing processes and to highlight any trends and to identify opportunities for product and/or process improvements.

- The extent of the quality reviews should be determined by the volume of the manufactured products and whether there have been changes introduced to the manufacturing process (i.e. the quality review needs to be more extensive when a high number of lots/ high product quantity has been produced than in case of low number of lots/ low product quantity; the quality review should also be more extensive when changes in the manufacturing process have been introduced during a given year than when no changes have been made).

- Quality reviews may be grouped by product type where scientifically justified. The manufacturer and -when it is a different legal entity- the marketing authorisation holder should evaluate the results of the review and assess whether corrective and/or preventive actions are required.

Based on the guidelines cat follows the assessment using risk-based approach

Risk-based approach: ATMPs are complex products and risks may differ according to the type of product, nature/characteristics of the starting materials and level of complexity of the manufacturing process. It is also acknowledged that the finished product may entail some degree of variability due to the use of biological materials and/or complex manipulation steps (e.g. cultivation of cells, manipulations that alter the function of the cells, etc.). In addition, the manufacture and testing of autologous ATMPs (and allogeneic products in a donor-matched scenario) poses specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material.

Considerations-ATMPs

Scientific innovation and technological development: ATMPs are at the forefront of scientific innovation and the field is experiencing rapid technological change that also impacts on the manufacturing processes. For instance, new manufacturing models are emerging to address the specific challenges of ATMPs (e.g. decentralised manufacturing for autologous products).

Additionally, ATMPs are also often developed in an academic or hospital setting operating under quality systems different to those typically required for the manufacture of conventional medicinal products.

Level of flexibility: It follows that, in laying down the GMP requirements applicable to ATMPs, it is necessary to recognise a certain level of flexibility so that the ATMP manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product.

This is particularly important in the case of investigational ATMPs, especially in early phases of clinical trials (phase I and phase I/II), due to the often incomplete knowledge about the product (e.g. potency) as well as the evolving nature of the routines (in order to adjust the manufacturing process to the increased knowledge of the product).

Application of the risk-based approach by ATMP manufacturers: The Risk-Based Approach ("RBA") is applicable to all type of ATMPS. It applies in an equal fashion to all type of settings. The quality, safety and efficacy attributes of the ATMPs and compliance with GMP should be ensured for all ATMPs, regardless of whether they are developed in a hospital, academic or industrial setting.

Quality of ATMPs: Manufacturers are responsible for the quality of the ATMPs they produce. The risk based approach permits the manufacturer to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality according to the specific risks of the product and the manufacturing process. While the risk-based approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.

Quality risks: The quality risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells/tissues, the biological characteristics of the vectors (e.g. replication competence or reverse transcription) and transgenes, the level and characteristics of the expressed protein (for gene therapy products), the properties of other non-cellular components (raw materials, matrixes) and the manufacturing process.

Assessment-control strategy: When identifying the control/mitigation measures that are most appropriate in each case, the ATMP manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (i.e. the totality of the control and mitigation measures applied) continues to be adequate.

Risk evaluation-updation of scientific knowledge: The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. Ultimately, this evaluation is linked to the protection of patients.

Documentation and standard operating procedures: The level of effort and documentation should be commensurate with the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

Regulatory strategies-communication with the authorities: The application of a risk-based approach can facilitate compliance but does not obviate the manufacturer's obligation to comply with relevant regulatory requirements and to demonstrate that it is able to adequately manage the risks of the product/manufacturing process. It likewise does not replace appropriate communications with the authorities.

Investigational ATMPs-consistency: The application of GMP to investigational ATMPs is intended to protect the clinical trial subjects and it is also important for the reliability of the results of the clinical trial, in particular by ensuring consistency of the product, that the results of the clinical trial are not

affected by unsatisfactory manufacturing used and that changes of the product throughout the development are adequately documented.

Quality data management: It is important to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of development. Therefore, a functional quality system should be in place for the manufacturing of investigational ATMPs.

Safety ensurance: The quality and safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the product and that the level of effort in the design and implementation of the strategy to ensure quality will step up gradually. It follows that the manufacturing procedures and control methods are expected to become more detailed and refined during the more advanced phases of the clinical trial.

Advice by the competent authorities: While the responsibility for the application of the risk-based approach lies with the manufacturer, it is encouraged that the advice of the competent authorities is sought in connection with the implementation of the risk-based approach for investigational ATMPs and, in particular, regarding early phases of clinical trials. The application of the risk-based approach should be consistent with the terms of the clinical trial authorisation. The description of the manufacturing process and process controls in the clinical trial authorisation application should explain, as appropriate, the quality strategy of the manufacturer when the risk-based approach is applied.

Alternative approaches-quality assurance: For aspects that are not specifically covered by the clinical trial authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented and to justify that the totality of the measures applied are adequate to ensure the quality of the product. In this regard, it is recalled that alternative approaches to the requirements explained in these Guidelines are only acceptable if they are capable of meeting the same objective.

Authorised ATMPs: For authorised ATMPs, the application of the risk-based approach should be consistent with the terms of the marketing authorisation. When providing the description of the manufacturing process and process controls in the marketing authorisation application (or, as appropriate, in the context of the submission of a variation), account can be taken of the specific characteristics of the product/manufacturing process to justify adaptation/deviation from standard expectations. Thus, the strategy to address specific limitations that may exist in connection with the manufacturing process, including controls of raw materials and starting materials, the manufacturing facilities and equipment, tests and acceptance criteria, process validation, release specifications, or stability data should be agreed as part of the marketing authorisation. For aspects that are not specifically covered by the marketing authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented when the risk-based approach is applied and to justify that the totality of the measures applied are adequate to ensure the quality of the product. In this regard, it is recalled that alternative approaches to the requirements explained in these Guidelines are only acceptable if they are capable of meeting the same objective. These guidelines adapt the EU GMP requirements to the specific characteristics of ATMPs and address the novel and complex manufacturing scenarios utilised for these products. They foster a risk-based approach to the manufacture and testing of such products. The Agency's Committee for Advanced Therapies (CAT) and GMDP Inspectors Working Group provided extensive input to the development of the guidelines.

GCP guidelines

Good Clinical Practice (GCP) is an intercontinental ethical and scientific quality standard for designing, recording and reporting trials that engage the participation of human subjects. Acquiescence with this standard provides public guarantee that the rights, safety and wellbeing of trial subjects are sheltered and that clinical-trial data are trustworthy.

Wma declaration of Helsinki ethical principles for medical research involving human subjects

Foreword:

- The Association (WMA) has developed the Declaration of Helsinki as a declaration of ethical principles for medical research involving human subjects, including research on identifiable human material and data. It is intended to be read as a whole in consideration of all other relevant paragraphs.

- Reliable with the directive of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages all human subjects to take on these principles.

General principles:

- The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

- It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

- Medical progress is based on research that ultimately must include studies involving human subjects.

- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

- Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

- While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

- It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

- Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

- Medical research should be conducted in a manner that minimises possible harm to the environment.

- Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

- Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, burdens and benefits:

- In medical practice and in medical research, most interventions involve risks and burdens.Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

- All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable groups and individuals:

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific requirements and research protocols:

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research ethics committees: The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and confidentiality: Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed consent:

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

- When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

- For medical research using identifiable human material or data, such as research on material or data contained in bio banks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of placebo: The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-trial provisions: In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research registration and publication and dissemination of results:

- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven interventions in clinical practice: In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Intercontinental clinical trials

Regardless of where they are conducted, all clinical trials included in applications for marketing authorisation in the EEA must be in accordance with:

- Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC.

- The ethical standards of the Clinical Trials Directive (Directive 2001/20/EC).

In July 1996, the EU adopted the guideline for good clinical practice, which lays out unified GCP standards for Europe, the United States of America and Japan.

GLP course of action

CAT in collaboration with the European Commission and the Clinical Trial Facilitation Group has developed a question and answer document on the GLP principles to be taken into account in relation to ATMPs:

Good Laboratory Practice (GLP) doctrine in relation to ATMPS:

- It is generally expected that non-clinical safety studies are carried out in conformity with the principles of GLP. However, it is recognised that, due to the specific characteristics of ATMPs, it would not always be possible to conduct these studies in conformity with GLP.

- Exploratory pre-clinical studies, where safety information is obtained alongside with other information (e.g. in dose finding studies), are also not expected to be conducted under GLP.

- If a pivotal non-clinical safety study 1 has not been conducted in conformity with the GLP principles; a proper justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data.

- When pivotal non-clinical safety studies are not conducted in compliance with GLP, detailed documentation of study conduct and archiving of data should be ensured. Additionally, the conduct of the study should be in accordance with a prospectively designed study protocol. A summary of deviations from the protocol and their potential impact on the outcome of the study should be included in the relevant study report. The sponsor of the non-clinical study should consider appointing a person responsible for the oversight of the conduct of the study and the study reports.

- Applicants who submit pivotal safety studies that are non-GLP compliant in the context of an application for a clinical trial or a marketing authorisation may be asked to submit additional data to justify the reliability of the studies or to permit a site visit to verify the conditions under which the study has been conducted.

Guidelines relevant for advanced therapy medicinal products: The European Medicines Agency develops scientific guidelines to help pharmaceutical companies and individuals to prepare marketing-authorisation applications for human medicines. This page lists relevant guidelines for applicants for advanced therapy medicinal products.

Multidisciplinary: Gene therapy: The European Medicines Agency's scientific guidelines on gene therapy help medicine developers prepare marketing authorisation applications for human medicines.

Specific guideline scenario

- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials.

- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products.

- Quality, preclinical and clinical aspects of gene therapy medicinal products.

- Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells.

- Development and manufacture of lentiviral vectors.

- Non-clinical studies required before first clinical use of gene therapy medicinal products.

- Non-clinical testing for inadvertent germline transmission of gene transfer vectors.

- Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products.

- Follow-up of patients administered with gene therapy medicinal products.

- Scientific requirements for the environmental risk assessment of gene-therapy medicinal products.

Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

Scientific advice questions are often related to the suitability of comparability proposals following changes to ATMP manufacturing processes or due to introduction of additional manufacturing sites. Manufacturing process changes may encompass improvements/change in equipment, raw materials and critical starting materials such as the cells or the vector or their suppliers, manufacturing process scale or product stability. Such changes are frequent, especially in the early stages of development of ATMPs. Every

change in manufacture should be done in accordance with GMP. The criticality of the changes and the estimation of their impact on the characteristics of the product should determine the amount of comparability data needed. Where applicable, the Variation Regulation [1] (for authorised ATMPs) or the clinical trial framework (for investigational ATMPs) should be followed. A suitable comparability program is required to support the introduction of changes during the development stages of an ATMP. The acceptable level of flexibility is progressively reduced from the non-clinical stage to the pivotal clinical use. Comparability is also an important tool to support changes after marketing authorisation where the process and the product are expected to be well defined and appropriately controlled by quality specifications and characterisation tools.

Cell-based advanced therapy medicinal products are complex in terms of composition and dynamic nature (e.g. different function, different differentiation stage, presentation in 3-dimensional forms). Also, the manufacturing process often depends on the combination of multiple biologically active reagents and manufacturing conditions that require careful consideration to ensure that the product remains the same for all patients treated. Changes are often necessary and include renewal of cell lots for production, modifications in the manufacturing process, changes of process scale, change of a raw material supplier, or proposals for additional manufacturing sites sharing the same manufacturing process. In all such cases the comparability exercise becomes a relevant tool to demonstrate that safety and efficacy data with a given preparation is also applicable after the change was introduced. The comparability program for these complex products cannot be based solely on the characterisation of the phenotypic markers related to purity confirming a heterogeneity profile. The dynamic nature of the product reflecting its metabolism, differentiation stage, structural organisation and interactions should be part of the comparability assessment. Functional / biological properties of the product are key to define the level of comparability attained as well as to define the extent of non-clinical and/or clinical data to be generated.

Vector based gene therapy medicinal products can be considered products more closely related to biotechnology in terms of manufacturing process and process controls. In this regard, ICH guideline Q5E can be more extensively considered and the comparability exercise can be focused on the capacity to address the changes with a careful analytical strategy. The present Q&A aims to address specific issues pertaining to the demonstration of comparability at the level of quality aspects for ATMPs.

Regulatory consideration. Changes to the manufacturing requirements registered as part of an ATMP marketing authorisation must be submitted and reviewed through variation procedures, as appropriate. This concept applies also to clinical trial authorisation of an investigational ATMP, for which substantial amendments must be presented.

EMA Role

- All advanced therapy medicines are authorised centrally *via* the European Medicines Agency (EMA).
- They benefit from a single evaluation and authorisation procedure.
- As with all medicines, the Agency continues to monitor the safety and efficacy of advanced therapy medicines after they are approved and marketed.
- The Agency also gives scientific support to developers to help them design pharmacovigilance and risk management systems used to monitor the safety of these medicines.
- Provides scientific advice to companies researching and developing new medicines;
- Preparing scientific guidelines and regulatory guidance to help pharmaceutical companies prepare marketing authorisation applications.
- Contributes to the harmonisation of regulatory requirements in the EU and internationally [1,2].

Committee for Advanced Therapies (CAT)

The Committee for Advanced Therapies (CAT) is the European Medicines Agency's (EMA) committee responsible for assessing the quality, safety and efficacy of Advanced Therapy Medicinal Products (ATMPs) and following scientific developments in the field.

It was established in accordance with Regulation (EC) No 1394/2007 on ATMPs as a multidisciplinary committee, gathering some of the best available experts in Europe [3].

Role of committee of advanced therapies

- The committee's main responsibility is to prepare a draft opinion on each ATMP application submitted to EMA, before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the marketing authorisation of the medicine concerned.
- At the request of EMA's Executive Director or the European Commission, the CAT can also draw up an opinion on any scientific matter relating to ATMPs.

The CAT

- Participates in certifying quality and non-clinical data for small and medium-sized enterprises developing ATMPs;
- Participates in providing scientific recommendations on the classification of ATMPs;
- Contributes to scientific advice, in cooperation with the Scientific Advice Working Party (SAWP);
- Takes part in any procedure delivering advice on the conduct of efficacy follow-up, Pharmacovigilance or risk-management systems for ATMPs;
- Advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy;
- Assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs;
- Provides scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs;
- Supports the work programmes of the CHMP working parties.

The CAT's work plan includes developing guidance documents, contributing to cross-committee projects, work on simplification of procedures and requirements for ATMPs, training for assessors and organising scientific workshops [3-5].

Conclusion

European Medicines Agency is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. EMA is governed by an independent Management Board. Its day-to-day operations are carried out by the EMA staff, overseen by EMA's Executive Director. EMA is a networking organisation whose activities involve thousands of experts from across Europe. These experts carry out the work of EMA's scientific committees. The Management Board consists of 36 members, appointed to act in the public interest, who do not represent any government, organisation or sector. The Board sets the Agency's budget, approves the annual work programme and is responsible for ensuring that the Agency works effectively and co-operates successfully with partner organisations across the EU and beyond. EMA has seven scientific committees that evaluate medicines along their lifecycle from early stages of development, through marketing authorisation to safety monitoring once they are on the market. In addition, the Agency has a number of working parties and related groups, which the committees can consult on scientific issues relating to their particular field of expertise. These bodies are composed of European experts made available by national competent authorities of the EU Member States, which work closely with EMA in the European medicines regulatory network. The Committee of Advanced therapies supports their helping hands

by assessment teams and multinational assessment teams, adopts a scientific opinion and intended to mobilise the best expertise for medicines evaluation and additional quality assurance of scientific assessments by peer review process, emphasizing on the commitment and strict follow-up of guidelines of GMP, GCP and GLP framed as a regulatory network. Thus The European Medicines Agency (EMA) is accountable for harmonising these standards at EU level. It also coordinates inspections to verify that medicine developers comply with them.

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